Pilot study: Role of anti-oxidants in the elicitation of contact allergic reaction to p-phenylenediamine (PPD).

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Pilot study to investigate the influence of pre-treatment with an anti-oxidant solution on the elicitation reaction (the occurrence of an allergic skin reaction after contact with an allergen) in subjects with a proven sensitization to PPD.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Observational invasive

Summary

ID

NL-OMON40582

Source
ToetsingOnline

Brief title
Anti-oxidants in PPD allergy

Condition

- Epidermal and dermal conditions

Synonym
Contact dermatitis, contact allergy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anti-oxidants, contact dermatitis, hairdye, PPD

Outcome measures

Primary outcome

The primary outcome is the difference in the result of the skin reaction on day 3 (72 hours) between the test area with only 2% PPD and the test area with pretreatment with the anti-oxidant solution, followed by 2% PPD.

Reading of the reactions will be accordance with the criteria of the ICDRG scored as -, ?, +, ++ or +++

Secondary outcome

The remaining test areas are control areas to exclude allergic reactions to other ingredients from the hair dye or the anti-oxidant solution.

Study description

Background summary

Allergic contact dermatitis is a T cell-mediated delayed type hypersensitivity induced by allergens such as PPD, resulting in a skin reaction. Stimulation with contact allergens generates ROS (reactive oxygen species) and causes oxidative degradation of hyaluronic acid. This results in indirect toll-like receptor activation and eventually amplification of the in*ammatory response resulting in a rash . The topical application of the antioxidant luteolin prevented sensitization and elicitation in a contact hypersensitivity (CHS) model (3). Induction of ROS and their role in the CHS response was identified by measurement of ROS production in dendritic cells in vitro and in vivo in murine skin (3,4). Antioxidants and hyaluronidase inhibitors were used to analyse the role of ROS and HA degradation in vitro and in vivo. Generation and degradation of hyaluronic acid as a result of ROS formation was studied in the skin by immunohistology.

Over a decade ago, Kuriyama et al demonstrated that vitamin E ointment at 20-40% suppressed allergic and irritant contact dermatitis in rats (5). This vitamin E ointment seemed to stabilize the keratinocytes and prevented the development of erythema.

Studies in mice demonstrated that topical pre-treatment with anti-oxidants prevents allergic contact dermatitis and even application of anti-oxidants after the contact with the allergen, prevented the allergic dermatitis (4). An explanation for this is the blockage of ROS. ROS crucially contributes to contact sensitizer induced skin inflammation and blocking of ROS production. This effectively inhibits contact hypersensitivity responses both in the sensitization as well as in the elicitation phase.

By applying an anti-oxidant cream before the usage of hair dye, the elicitation reaction might be diminished by the inhibition of ROS and result in no or a less severe skin reaction to PPD.

A simple self-test with a patch on their forearm may give an indication about such a contact-allergy, which was investigated in a pilot study conducted in the UMCG in 2007. A use test of 30 minutes was enough to demonstrate a positive reaction in 53-60% of the subjects with a ++ reaction in the past and in 93-100% of the patients with a +++ reaction.

An unpublished study in humans demonstrated a reduction of elicitation response to 0.1%, 0.5%, 1% hair dye and 1% PPD after pretreatment with vitamin C. However, the procedures used in this study, were not standardized. In addition, the use condition of 2% PPD was not used in the previous study. Therefore we would like to study the effect of a vitamin C product (pre)treatment on elicitation reaction to hair dye product with 2% PPD.

The current study will apply the same protocol as the pilot study from 2007, but will in addition to the use test for hair dyes, include a pretreatment with an anti-oxidant solution. Anti-oxidants are expected to prevent the elicitation reaction due to coupling between the PPD and the anti-oxidant, which makes the PPD less likely to penetrate the skin.

(1) Thyssen JP, White JM, European Society of Contact Dermatitis. Epidemiological data on consumer allergy to p-phenylenediamine. Contact Dermatitis 2008:59:327-343.
(2) McFadden JP, White IR, Frosch PJ, Sosted H, Johansen JD, Menne T. Allergy to hair dye. BMJ 2007:334:220.
(3) Esser PR, Woelfle U, Jakob T, Schempp CM, Martin SF. Linking ROS production and HA degradation - A crucial role for the generation of endogenous ligands in CHS responses to contact sensitizers. Experimental Dermatology 2011:20:177.
(4) Esser PR, Wolfle U, Durr C, von Loewenich FD, Schempp CM, Freudenberg MA, et al. Contact sensitizers induce skin inflammation via ROS production and hyaluronic acid degradation. PLoS One 2012:7:e41340.

(5) Kuriyama K, Shimizu T, Horiguchi T, Watabe M, Abe Y. Vitamin E ointment at high dose levels suppresses contact dermatitis in rats by stabilizing keratinocytes. Inflamm Res 2002:51:483-489.

Study objective

Pilot study to investigate the influence of pre-treatment with an anti-oxidant solution on the elicitation reaction (the occurrence of an allergic skin reaction after contact with an allergen) in subjects with a proven sensitization to PPD.

Study design

For this study, we aim to include the same subjects as in the pilot study, given the fact that they have been extensively tested and documented. In total 30 subjects will be included.
A short interview will be held to confirm the inclusion and exclusion criteria. Since the included subjects already participated in a similar patch-testing study before, this will only be a short check. Special attention will be paid to new immunosuppressive medication and pregnancy will be excluded by history. No clinical tests will be performed to exclude pregnancy or co-morbidity. The volar side of the forearms will be inspected for active skin disease by means of physical examination.

Eight different test areas are marked on the volar aspects of the forearms (4 on each arm from 2 by 2 cm). The anti-oxidant cream will be applied to three test areas and the anti-oxidant free cream will be applied to three other test areas. Two test areas will not be pre treated. After 10 minutes 0% and 2% PPD hair dye cream will be applied to 6 out of the 8 test areas for 30 minutes, resulting in 8 different combinations:
o 30 minutes 0% PPD hair dye cream mixed with hydrogen peroxide
o 30 minutes 2% PPD hair dye cream mixed with hydrogen peroxide
o 10 minutes antioxidant cream followed by 30 minutes 0% PPD hair dye cream mixed with hydrogen peroxide (in total 40 minutes antioxidant cream)
o 10 minutes antioxidant cream followed by 30 minutes 2% PPD hair dye cream mixed with hydrogen peroxide (in total 40 minutes antioxidant cream)
o 10 minutes antioxidant-free cream followed by 30 minutes 0% PPD hair dye cream mixed with hydrogen peroxide (in total 40 minutes antioxidant-free cream)
o 10 minutes antioxidant-free cream followed by 30 minutes 2% PPD hair dye cream mixed with hydrogen peroxide (in total 40 minutes antioxidant-free cream)
o 40 minutes antioxidant cream
o 40 minutes antioxidant-free cream

The hair dye is a 1:1 mixture of 4 % PPD, 3,6% 2-methylresorcinol and 1,9% 2-methyl-5-hydroxyethylaminophenol in a basic cream with a 6% solution of water peroxide. The total PPD concentration is 2%, which is comparable to normal use

conditions and the conditions used in the pilot study of 2008. The 0% PPD hair dye cream is a negative control, which is the same mixture as the 2% PPD cream, only without PPD, and with 2-methylresorcinol and 2-methyl-5-hydroxyethylaminophenol. 2-Methylresorcinol and 2-methyl-5-hydroxyethylaminophenol are added as couplers to the hair dye cream and selected because of their low-sensitization abilities. The basic cream is Koleston Perfect Chassis without fragrances. The ingredients of this cream are used in various cosmetics (Lanette O, Dusoran MD, Na-laurylethersulfaat, Na-cocoyl isethionate, EDTA, Na-sulfite, Ascorbinezuur, Ammonia, Na-hydroxide, Water).

Forty minutes after the first application, all test areas are rinsed off and washed with water and shampoo (Andrélon, Iedere dag shampoo, Unilever). Fifteen minutes after the rinsing (55 minutes after application) the first reading of the test areas is performed according to the guidelines of the International Contact Dermatitis Research Group. Recordings of clinical manifestations will be made. All the tested skin areas will be photographed. During the study subjects are allowed to continue their daily activities, with the advice to minimize exposure to sunlight of the tested skin areas until after visit 3 and extensively rub the test areas. They are allowed to shower, swim or sport if this is part of their normal routine.
Total duration: 60 minutes

Visit 2, day 2, 48 hours after application
After 48 hours the eight tested skin areas will be inspected again for possible reactions according to the criteria of the International Contact Dermatitis Research Group. Recordings of clinical manifestations will be made. All the test areas will be photographed.
Total duration: 15 minutes.

Visit 3, day 3, 72 hours after application
On day 3 the tested skin areas will be inspected once more for possible reactions according to the criteria of the International Contact Dermatitis Research Group. Recordings of clinical manifestations will be made. All the test areas will be photographed.

Study burden and risks

On the day of the patch-test application the time burden will be 60 minutes at the most, in addition to travel time. The actual application of the patch will cause minimal discomfort. The time burden for reading the patch test reaction will be less than 15 minutes on day 2 and day 3. There will be a travel time burden, but the participants are offered the opportunity to perform the readings at a place of their preference (at their home or at work for example).

Participants might develop a skin reaction due to the PPD. This can exist of redness, possibly with some itching, vesicles and papules, at the site of the

patch-test with the PPD containing solution. This skin reaction is transient, and will disappear within a few days. Participants have the option to receive a one-time application of a corticosteroid-containing cream to enhance the remission of the reaction. Systemic effects from resorption of PPD are irrelevant at such a short exposure time and small application area.

All the products used in this study are cosmetics according to the EU definition: any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.
The cosmetics are used well within the normal range of use.

Participants will receive gift cards with a value of ¤100,- and reimbursement of travel expenses.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• A history of (mild, moderate or severe) allergic contact dermatitis after exposure to a PPD-containing product (mostly hair dye)
• A positive patch-test to PPD (1% in white petrolatum)
• Adulthood (>=18 years)
• Legal competence
• Participated in one of the previous studies from the UMCG concerning PPD (METc 2007.230)

Exclusion criteria

- Skin anomalies on the forearm
- Severe skinanomalies elsewhere on the body
- Immunosuppressive medication during or in the previous 4 weeks of the study
- (wish to become) pregnant
- Legally incompetent

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2014
Enrollment:	22

Type:	Actual

Ethics review

Approved WMO Date:	09-05-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL46121.042.13